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Enhanced biomedical heat-triggered carriers via nanomagnetism tuning in ferrite-based nanoparticles

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ABSTRACT

Biomedical nanomagnetic carriers are getting a higher impact in therapy and diagnosis schemes while their constraints and prerequisites are more and more successfully confronted. Such particles should possess a well-defined size with minimum agglomeration and they should be synthesized in a facile and reproducible high-yield way together with a controllable response to an applied static or dynamic field tailored for the specific application. Here, we attempt to enhance the heating efficiency in magnetic particle hyperthermia treatment through the proper adjustment of the core–shell morphology in ferrite particles, by controlling exchange and dipolar magnetic interactions at the nanoscale. Thus, core–shell nanoparticles with mutual coupling of magnetically hard ($CoFe_2O_4$) and soft ($MnFe_2O_4$) components are synthesized with facile synthetic controls resulting in uniform size and shell thickness as evidenced by high resolution transmission electron microscopy imaging, excellent crystallinity and size monodispersity. Such a magnetic coupling enables the fine tuning of magnetic anisotropy and magnetic interactions without sparing the good structural, chemical and colloidal stability. Consequently, the magnetic heating efficiency of $CoFe_2O_4$ and $MnFe_2O_4$ core–shell nanoparticles is distinctively different from that of their counterparts, even though all these nanocrystals were synthesized under similar conditions. For better understanding of the AC magnetic hyperthermia response and its correlation with magnetic-origin features we study the effect of the volume ratio of magnetic hard and soft phases in the bimagnetic core – shell nanocrystals. Eventually, such particles may be considered as novel heating carriers that under further biomedical functionalization may become adaptable multifunctional heat-triggered nanoplatforms.

1. Introduction

Biomedical nanomagnetics is a truly integrated, multidisciplinary area of research in science since chemistry, materials science, physics, engineering, biology and medicine are incorporated. Recent developments offer exciting possibilities in personalized medicine, with broad applications in imaging, diagnostics and therapy. Biomedical applications require magnetic nanoparticles (MNPs) with several well-defined and reproducible structural, physical, and chemical features. A major goal of such a project is the fine-tuning of the synthesis concluding to refinement of the magnetic behavior at the nanoscale with emphasis on the relaxation dynamics and surface functionalization of magnetic nanoparticles. The ability of nanotechnology to interact with matter at the molecular scale provides not only the possibility to ascertain the molecular constituents of a disease, but also the way in which these constituents affect the totality of a biological function. The capacity to incorporate an array of structural and chemical functionalities onto the same nanoscale architecture should also enable more accurate, sensitive and precise screening and cure of diseases which appear with significant pathological heterogeneity such as cancer. Despite the fact, that magnetic nanoparticles are attracting considerable and unceasing interest for their biomedical applicability, materials related research projects and clinical practice do not seem to be following fully compatible pathways [1]. In the quest for biomedical nanomagnetic carriers

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there are several constraints and prerequisites that should be confronted prior to their actual implementation in therapy and/or diagnosis schemes [2]. Starting from the particles themselves, they should first of all possess a well-defined size with minimum agglomeration and they should be synthesized in a facile and reproducible high-yield way. They need to provide a controllable response to an applied static or dynamic field tailored for the specific application. This may be achieved complementarily by tuning magnetic interactions in the collective behavior without sparing the good structural, chemical, colloidal stability under different pH and redox conditions of the biological environment [3]. Obviously, for biomedical applications, nanoparticles should be non-toxic materials or adequately coated to ensure biocompatibility and prevent non-specific reactions with the medium. They should also facilitate the attachment of functional groups for applications based on biological interactions in order to be considered as theranostics platforms [4].

Magnetically induced heat generation from nanoparticles can be used for various purposes initiating from a disease therapy known as hyperthermia. Materials combination and external stimuli (frequency, magnetic field amplitude, gradient direction) allow the proper adjustment of thermal parameters. Hyperthermia is currently regarded as the least-invasive approach in cancer therapy while it may be combined with biomolecular functionalities and offer additional beneficial features such as low dosage due to localization, remote control and on-demand actuation [5]. Moreover, the conversion of electromagnetic energy into heat by nanoparticles can initiate heat-triggered procedures such as drug release and remote control of single cell functions. So far, poor conversion efficiencies have hindered practical applications, since for example drug release and remote control of single cell functions currently require stronger heating conversion efficiency as indicated by AC field application schemes [6,7]. Upon exposure to an alternating external magnetic field the magnetic nanoparticles continuously emit heat via relaxation loss (Néel and/or Brown) and/or hysteresis loss pathways depending on their magnetic profile. The specific loss power (SLP), a quantifiable index of the conversion efficiency, has to be maximized by tuning the particle and field features, since it is strongly dependent on size, composition, magnetic profile, field intensity and frequency [8]. The strategy for enhancing SLP is crucial, because higher SLP values result to better efficiency with lower dosage level of nanoparticles and shorter treatment duration. Among the particle features, size and its polydispersity (s), saturation magnetization (M_s) and magnetic anisotropy (K_{eff}) seem to be the key factors to optimize particles' response under external field application [9].

In an attempt to develop novel heat mediators with high thermal energy transfer capability, we have been recently examining the effects of size and composition on the magnetic heating power of ferrite magnetic nanoparticles (MFe_2O_4, M=Fe, Ni, Co, Mn) [10,11] and their combinatory approaches as hyperthermia and drug agents [12,13]. The choice of ferrite nanoparticles is based on their low inherent toxicity, ease of synthesis, physical and chemical stability and tunable magnetic properties [14]. For instance, $MnFe_2O_4$ is a suitable ingredient as an enhanced MRI contrast agent [1]. On the other hand, $CoFe_2O_4$, is a representative hard material ($K_{eff}=2.0\times10^5$ J/m^3) able to generate an exchange coupled nanoscale element with tunable magnetic anisotropy if properly coupled to a representative soft material such as $MnFe_2O_4$ ($K_{eff}=3.0\times10^3$ J/m^3). Since the magnetic anisotropy constant K_{eff} is an intrinsic materials property, it is a challenging task to tune anisotropy values of individual nanoparticles as desired. An exchange-coupled nanomagnet by means of interfacial exchange interaction between hard and soft phases has the potential to exhibit tunable magnetism.

Aiming to control nanoscale magnetism, in this manuscript we examine core–shell structures (with a magnetically hard core and magnetically soft shell or vice/versa) encompassing concepts of surface and exchange anisotropy while reflecting morphology and structure effect on the magnetic properties of the nanoparticle [15] and on AC the heating efficacy [16]. Because of the facile synthetic controls that result in nanoparticles with uniform size and shell thickness, excellent crystallinity and size monodispersity, such a magnetic coupling allows for optimal tuning of anisotropy constant K_{eff}. Firstly, nanoparticles were synthesized by standard wet chemistry methodologies (i.e. thermal decomposition) that satisfy the requirements of simple and reproducible synthetic protocols with high monodispersity and small size distributions ($s<5\%$). Particles possess tunable magnetic properties approaching bulk values depending on size. Since SLP strongly depends on particle (size, composition and magnetic profile) and field (intensity and frequency) parameters, it was selected as the criterion to monitor-optimize particle performance. Secondly, core–shell magnetic nanoparticles are synthesized, characterized and with the constituent conventional single-phase nanoparticles.

2. Experimental procedures

Solutions of magnetic nanoparticle were prepared via standardized wet chemistry methodologies [17] based on the thermal decomposition of molecular precursors. The reagents manganese (II)-acetate tetrahydrate, cobalt(II)-acetate tetrahydrate, iron(III)-acetylacetonate, oleic acid (technical grade 90%), and octadecene (technical grade 90%) were purchased from Aldrich, ethanol absolute and acetone absolute from VWR, toluene from Merck and tetrahydrofuran (THF) from Riedel-de-Haen. Table 1 lists the samples, the relevant ingredients and quantities used for their synthesis. Samples S1 and S2 are Mn and Co ferrite single-phase magnetic nanoparticles, respectively. These first two reference samples (S1–S2) were synthesized by dissolving the proper precursors ($Fe(acac)_3$ and either $Mn(CH_3COO)_2$ for S_1 or $Co(CH_3COO)_2$ for S_2) together with oleic acid acting as a surfactant. At the second stage, the synthesized S1, S2 MNPs were also used as seed materials to form core–shell nanoparticles and to check the intermixing efficiency in the synthetic processes of the bimagnetic ferrite samples (S3 and S4). In more detail, for the sample S3 (core–shell nanoparticles) the $MnFe_2O_4$ synthetic procedure of sample S1 was repeated together after the addition of 78 mg dried $CoFe_2O_4$-particles to act as cores for the core–shell morphology

Table 1
Notation of samples, parameters and deliverables of wet chemistry methodology.

Sample	*Ingredients and quantities*	*Magnetic Nanoparticles*
S1	*2 mmol $Mn(CH_3COO)_2$, 4 mmol $Fe(acac)_3$, 18 mmol oleic acid*	*$MnFe_2O_4$*
S2	*2 mmol $Co(CH_3COO)_2$, 4 mmol $Fe(acac)_3$, 18 mmol oleic acid*	*$CoFe_2O_4$*
S3	*78 mg dried $CoFe_2O_4$-particles, 1 mmol $Mn(CH_3COO)_2$, 2 mmol $Fe(acac)_3$, 9 mmol oleic acid and 9 mmol oleylamine*	*shell: $MnFe_2O_4$ core: $CoFe_2O_4$*
S4	*78 mg dried $MnFe_2O_4$-particles, 1 mmol $Co(CH_3COO)_2$, 2 mmol $Fe(acac)_3$, 9 mmol oleic acid, 4.5 mmol oleylamine, 4.5 mmol tetraoctylamine*	*shell: $CoFe_2O_4$ core: $MnFe_2O_4$*

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